



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>5</sup> :  A61K 9/12, 9/72	A1	(11) International Publication Number: WO 91/11173  (43) International Publication Date: 8 August 1991 (08.08.91)									
<p>(21) International Application Number: PCT/GB91/00133</p> <p>(22) International Filing Date: 30 January 1991 (30.01.91)</p> <p>(30) Priority data:</p> <table border="0"><tr><td>9002351.6</td><td>2 February 1990 (02.02.90)</td><td>GB</td></tr><tr><td>9023655.5</td><td>31 October 1990 (31.10.90)</td><td>GB</td></tr><tr><td>9026476.3</td><td>5 December 1990 (05.12.90)</td><td>GB</td></tr></table> <p>(71) Applicant (for all designated States except US): FISONS PLC [GB/GB]; Fiston House, Princes Street, Ipswich, Suffolk IP1 1QH (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): STEELE, Gerald [GB/GB]; 13 Ashleigh Drive, Loughborough, Leicestershire LE11 3HN (GB). SOMANI, Asit [GB/GB]; 29 Glebe Street, Loughborough, Leicestershire LE11 1JR (GB). LIM, Joseph, Geok, Paan [MY/GB]; 17 Windsor Drive, Shepshed, Leicestershire LE12 9QR (GB).</p>		9002351.6	2 February 1990 (02.02.90)	GB	9023655.5	31 October 1990 (31.10.90)	GB	9026476.3	5 December 1990 (05.12.90)	GB	<p>(74) Agent: GILHOLM, Stephen, Philip; Fisons plc, 12 Derby Road, Loughborough, Leicestershire LE11 0BB (GB).</p> <p>(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.</p> <p>Published</p> <p><i>With international search report.</i></p> <p><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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<p>(54) Title: PROPELLANT COMPOSITIONS</p> <p>(57) Abstract</p> <p>Pressurised aerosol composition comprising a liquified hydrofluorocarbon propellant containing substantially no non-hydrofluorocarbon solvent, having dispersed therein a medicament and a fluorinated surfactant. Preferred surfactants include FC 430 and FC 431.</p>											

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### Propellant Compositions

This invention relates to pressurised aerosol compositions, in particular compositions of inhalation medicaments.

5 Pressurised aerosols for the administration of medicaments, and indeed for other applications, conventionally contain one or more liquified chlorofluorocarbons (CFC's) as propellant. Such materials are suitable for use in such applications since they have  
10 the right vapour pressures (or can be mixed in the right proportions to achieve a vapour pressure in the right range) and are essentially taste- and odour-free.

In recent years there has been increasing concern about the depletion of the ozone layer in the upper  
15 atmosphere. This is believed to be due to the release into the atmosphere of CFC's and has led to a search for alternative agents for use in all applications of CFC's. To this end, aerosols for many applications are now pressurised using pressurised gases such as nitrogen or  
20 hydrocarbons. However, such propellants are generally not suitable for use in the administration of inhalation medicaments since they are toxic and/or the pressure within the canister falls each time the device is used which leads to unreproducible dosing.

25 The use of hydrofluorocarbons as aerosol propellants

has also been suggested. European Patent Application 0 372 777, published after the earliest priority date of this application, states that the use of the hydrofluorocarbon propellant 134a and drug as a binary mixture or in combination with a conventional surfactant such as sorbitan trioleate does not provide formulations having suitable properties for use with pressurised inhalers and suggests that satisfactory formulations may be made by adding a compound having a higher polarity than propellant 134a, such as pentane or ethanol. It is stated that the addition of a compound of higher polarity than propellant 134a to propellant 134a provides a mixture in which increased amounts of surfactant may be dissolved compared to their solubility in propellant 134a alone. It is further stated that the presence of increased amounts of solubilised surfactant allows the preparation of stable, homogenous suspensions of drug particles. The use of such co-solvents is undesirable since they may have unsuitable properties, for example, they may be flammable and/or toxic.

US Patent No 4352789 suggests the use of perfluorinated surfactants which are insoluble in CFC or perfluorinated propellants as a coating for finely divided medicament to be formulated in CFC or perfluorinated propellants.

Surprisingly, we have now found that mixtures of

hydrofluorocarbons and fluorinated surfactants have properties which render them suitable for use as propellant systems for aerosol compositions.

Thus, according to the invention there is provided a  
5 pressurised aerosol composition comprising a liquified hydrofluorocarbon propellant containing substantially no non-hydrofluorocarbon solvent, having dispersed therein a medicament and a fluorinated surfactant.

The compositions according to the invention are  
10 advantageous in that the solubility of the surfactant is such as to ensure good dispersion of the medicament and smooth operation of the aerosol valve. In particular, and in contrast to EP-A-0 372 777, the surfactants which characterise the present invention are sufficiently soluble  
15 in hydrofluorocarbons to enable them to be used without the presence of an additional substance as co-solvent.

The propellant mixtures of the present invention may also be advantageous in that they are substantially taste- and odour-free and have suitable vapour pressures for the  
20 administration of medicaments by inhalation, yet are environmentally safe and acceptable, especially when compared with compositions including chlorofluorocarbons. In addition, they may be less irritant than corresponding compositions including conventional surfactants such as  
25 oleic acid and sorbitan trioleate.

A wide range of fluorinated surfactants may be used in the compositions of the present invention. The surfactant may be perfluorinated or otherwise.

Perfluorinated surfactants which may be used include  
5 ionic surfactants, both anionic and cationic, eg  
perfluorinated alcohol phosphate esters and their salts,  
perfluorinated sulphonamide alcohol phosphate esters and  
their salts, and perfluorinated alkyl sulphonamide alkylene  
quaternary ammonium salts. However, we prefer surfactants  
10 which are non-ionic.

Other surfactants may be used which, while not perfluorinated as such, contain at least one perfluorinated alkyl group.

We prefer surfactants which contain at least one  
15 (CF<sub>2</sub>) group, more preferably from 2 to 60, eg 5 to 20  
such groups.

We prefer surfactants which contain one or more ether or carboxylic ester linkages, more preferably from 2 to 60, eg 4 to 10 such linkages. We particularly prefer compounds  
20 which contain both ether and ester linkages.

We prefer surfactants which contain at least one (CH<sub>2</sub>) group, more preferably from 2 to 60, eg 5 to 20 such groups. We further prefer surfactants which contain at least one (OCH<sub>2</sub>CH<sub>2</sub>) group, more preferably from 2 to  
25 30, eg 3 to 10 such groups.

Preferred non-ionic surfactants include, for example fluorinated alcohols, esters, amides, N-oxides or sulphonamides. We particularly prefer polyfluoroalkoxyethylenes of the general formula

5  $C_mF_{2m+1}CH_2(OC_2H_4)_nOH$  in which m is an integer from 7 to 18 and n is an integer from 2 to 6. Other preferred surfactants include:



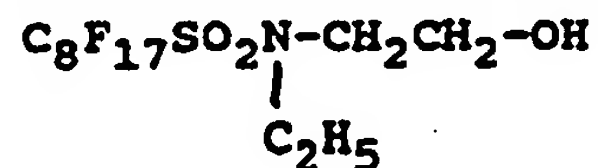
10 in which z is an integer from about 2 - 20,



in which n is an integer from about 10 - 60.

Further examples of preferred surfactants are the following:

15 The fluoroaliphatic polymeric esters known as FC 430 and FC 431, available from 3M. These are believed to be acrylic polymers having a fluorinated portion based on



20 and a portion including an ethylene/propylene oxide block copolymer. These surfactants may be supplied as a 50:50 mixture with ethyl acetate, the latter compound being preferably removed before the surfactant is used in accordance with the present invention.

25 Other fluorinated surfactants produced by 3M that may

be mentioned include FC 170c, FC 171 and FC 807. We particularly prefer surfactants which have both a fluorinated portion, especially a perfluorinated portion, and a hydrophilic portion, eg a portion based on an ethylene and/or propylene oxide.

Other fluorinated surfactants which may be mentioned are ethyl perfluorooctylsulphonamide, the linear perfluoropolyether known as Fomblin-M, perfluorodecalin and tris(1H,1H,5H-octafluoropentyl)phosphate. All of these are available from Fluorochem Ltd.

Mixtures of fluorinated surfactants may also be used, eg mixtures of two or more of the fluorinated surfactants listed above. Alternatively, mixtures may be used of one or more fluorinated surfactants with one or more of the surfactants conventionally used in aerosol compositions, eg CFC-pressurised compositions. Examples of such conventional surfactants are: natural oils, sorbitan oleates, eg monooleate and trioleate, sorbitan monolaurate, monoglycerides, eg glyceryl monooleate, monostearate and monolaurate, lecithins, oleic acid, etc.

Other surfactants and adjuvants that may be added include poloxamers and/or polyethylene glycols, eg PEG 1000 and PEG 1500.

In the present context, the term 'hydrofluorocarbon' is to be taken to mean a compound of general formula





in which x is an integer from 1 to 3,  $y+z=2x+2$  and y and z are both at least 1.

Particular hydrofluorocarbons of interest are

5  $CF_3CFH_2$  (Propellant 134a),  $CH_3CHF_2$  (Propellant 152a) and  $CF_3CHFCF_3$  (Propellant 227). We particularly prefer compositions including propellant 227.

In general the vapour pressure of the mixture should be in the range suitable and permitted for aerosol  
10 propellants. The vapour pressure may be varied by mixing one or more hydrofluorocarbons and/or some other suitable vapour pressure modifying agent in appropriate proportions.

We prefer the vapour pressure of the mixture to be in the range 20 to 100 psi, more preferably 40 to 80 psi, eg  
15 about 60 psi.

The amount of surfactant in the composition will generally be from about 0.01 to 10% by weight, more preferably from about 0.1 to 5%, eg about 1%.

The medicament may be in solid, particulate form (ie  
20 the composition may be a suspension), or the active ingredient may be dissolved in the propellant.

Medicaments which may be dispersed in the propellant mixture according to the invention include any medicaments which are conventionally administered by inhalation of a  
25 pressurised aerosol formulation. Such medicaments include

drugs for use in the prophylactic or remedial treatment of reversible obstructive airways disease, eg drugs such as sodium cromoglycate, nedocromil sodium, inhaled steroids, eg beclomethasone dipropionate, fluticasone and tipredane, and bronchodilators, eg salbutamol, reproterol, 5 terbutaline, fomoterol, pirbuterol, isoprenaline, salmeterol, fenoterol and salts thereof, and anticholinergic agents such as ipratropium bromide and atropine.

Where the active ingredient is solid, it preferably 10 has a particle size distribution such that a high proportion of the particles are of a size capable of penetrating deep into the lung. In particular, the active ingredient is preferably in a form having a mass median diameter of from 0.1 to 10  $\mu\text{m}$ , more preferably from 0.1 15 to 4  $\mu\text{m}$ , eg about 2 or 3  $\mu\text{m}$ .

We prefer the medicament to have a mass median diameter in the range 0.01 to 10 microns, more preferably from 1 to 5 microns. The composition preferably comprises from 0.01 to 15, preferably from 0.1 to 10, and most 20 preferably from 0.5 to 5% w/w medicament.

In producing the compositions according to the invention, a container equipped with a valve is filled with a propellant containing the finely-divided medicament. The container may first be charged with a weighed amount of 25 medicament which has been ground to a predetermined

particle size, or with a slurry of powder in the cooled liquid propellant. The container may alternatively be filled by introducing powder and propellant by the normal cold filling method, or a slurry of the powder in one component of the propellant may be placed in the container, the valve sealed in place, and the balance of the propellant then introduced by pressure filling through the valve nozzle. As a further alternative a bulk quantity of the total composition may be filled into the container through the valve.

The invention will now be illustrated, but in no way limited, by the following Example.

Example

Compositions of the were prepared by cold filling of the ingredients into aluminium aerosol canisters which were then sealed by crimping a 50 $\mu$ l or 100 $\mu$ l aerosol valve in place.

The following combinations of micronised active ingredient, surfactant and propellant were used, removing solvent from the surfactant where necessary:

1. Nedocromil sodium	0.200g
FC 431	0.061g
Propellant 134a	11.979g

	2.	Tipredane	0.100g
		FC 431	0.071g
		Propellant 227	13.949g
5	3.	Sodium cromoglycate	0.200g
		FC 430	0.061g
		Propellant 134a	11.979g
	4.	Sodium cromoglycate	0.200g
10		FC 430	0.071g
		Propellant 227	13.849g
	5.	Nedocromil sodium	0.200g
		FC 430	0.061g
15		Propellant 134a	11.979g
	6.	Nedocromil sodium	0.200g
		FC 430	0.071g
		Propellant 227	13.849g
20	7.	Salbutamol sulphate	0.040g
		FC 431	0.061g
		Propellant 134a	12.139g

8.	Fenoterol hydrobromide	0.040g
	FC 430	0.071g
	Propellant 227	14.009g

5      In all cases stable suspensions of the active  
ingredient in the propellant were obtained.

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## Claims

1. A pressurised aerosol composition comprising a liquified hydrofluorocarbon propellant containing substantially no non-hydrofluorocarbon solvent, having dispersed therein a medicament and a fluorinated surfactant.
2. A composition according to claim 1, wherein the surfactant is a non-ionic surfactant.
3. A composition according to claim 1 or 2; wherein the surfactant contains at least one (CF<sub>2</sub>) group.
4. A composition according to any one of claims 1, 2 or 3, wherein the surfactant contains one or more ether or carboxylic ester linkages.
5. A composition according to any one of the preceding claims, wherein the surfactant contains at least one (CH<sub>2</sub>) group.
6. A composition according to any one of the preceding claims, wherein the composition includes an additional surfactant selected from poloxamers and polyethylene glycols.
7. A composition according to any one of the preceding claims, wherein the propellant is CF<sub>3</sub>CFH<sub>2</sub>, CH<sub>3</sub>CHF<sub>2</sub>, CF<sub>3</sub>CHFCF<sub>3</sub> or mixtures thereof.
8. A composition according to any one of the preceding claims, wherein the medicament is sodium cromoglycate,

nedocromil sodium, beclomethasone dipropionate,  
fluticasone, tiotropium bromide, atropine or a  
bronchodilator selected from salbutamol, reproterol,  
terbutaline, formoterol, pirbuterol, isoprenaline,  
5 salmeterol, fenoterol or a salt of any one thereof.

9. A composition according to any one of the preceding  
claims, comprising from 0.01 to 10% by weight of  
fluorinated surfactant.

10. A composition according to any one of the preceding  
10 claims, comprising from 0.01 to 15% w/w medicament.

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# INTERNATIONAL SEARCH REPORT

International Application No **PCT/GB 91/00133**

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) * According to International Patent Classification (IPC) or to both National Classification and IPC <b>IPC<sup>5</sup>: A 61 K 9/12, 9/72</b>																	
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; font-size: small;">Minimum Documentation Searched †</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 25%; border: none; vertical-align: top;"> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 50%; font-size: small;">Classification System</th> <th style="width: 50%; font-size: small;">Classification Symbols</th> </tr> <tr> <td style="text-align: center; vertical-align: middle; padding: 10px;"><b>IPC<sup>5</sup></b></td> <td style="text-align: center; vertical-align: middle; padding: 10px;"><b>A 61 K</b></td> </tr> </table> </td> <td style="border: none;"></td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched ‡</div>			<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 50%; font-size: small;">Classification System</th> <th style="width: 50%; font-size: small;">Classification Symbols</th> </tr> <tr> <td style="text-align: center; vertical-align: middle; padding: 10px;"><b>IPC<sup>5</sup></b></td> <td style="text-align: center; vertical-align: middle; padding: 10px;"><b>A 61 K</b></td> </tr> </table>	Classification System	Classification Symbols	<b>IPC<sup>5</sup></b>	<b>A 61 K</b>										
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<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT †</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; font-size: small;">Category *</th> <th style="width: 60%; font-size: small;">Citation of Document, †† with indication, where appropriate, of the relevant passages ‡‡</th> <th style="width: 30%; font-size: small;">Relevant to Claim No. ‡‡</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>P,X</b></td> <td style="padding: 5px;"> <b>WO, A, 9007333 (RIKER LABORATORIES)</b>            12 July 1990            see abstract; page 2, line 28 - page 3, line 4; page 4, line 1 - page 6, line 26; claims 1,5,6,8,11-14         </td> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>1-5,7,9,10</b></td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>X</b></td> <td style="padding: 5px;"> <b>US, A, 4352789 (THIEL)</b>            5 October 1982            see abstract; column 2, line 34 - column 3, line 50; column 3, line 61 - column 4, line 16; column 5, lines 3-54; column 6, lines 21-38; examples 11,23-26; claims 1,5-13         </td> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>1-5,8-10</b></td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>Y</b></td> <td style="padding: 5px;"> <b>cited in the application</b>  <div style="text-align: center;">--</div> </td> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>6,7</b></td> </tr> <tr> <td colspan="3" style="text-align: center; padding: 20px 0;">./.</td> </tr> </tbody> </table>			Category *	Citation of Document, †† with indication, where appropriate, of the relevant passages ‡‡	Relevant to Claim No. ‡‡	<b>P,X</b>	<b>WO, A, 9007333 (RIKER LABORATORIES)</b> 12 July 1990 see abstract; page 2, line 28 - page 3, line 4; page 4, line 1 - page 6, line 26; claims 1,5,6,8,11-14	<b>1-5,7,9,10</b>	<b>X</b>	<b>US, A, 4352789 (THIEL)</b> 5 October 1982 see abstract; column 2, line 34 - column 3, line 50; column 3, line 61 - column 4, line 16; column 5, lines 3-54; column 6, lines 21-38; examples 11,23-26; claims 1,5-13	<b>1-5,8-10</b>	<b>Y</b>	<b>cited in the application</b> <div style="text-align: center;">--</div>	<b>6,7</b>	./.		
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<div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 45%;">           * Special categories of cited documents: ††            "A" document defining the general state of the art which is not considered to be of particular relevance            "E" earlier document but published on or after the international filing date            "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)            "O" document referring to an oral disclosure, use, exhibition or other means            "P" document published prior to the international filing date but later than the priority date claimed         </div> <div style="width: 45%;">           † later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention            "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step            "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art            "A" document member of the same patent family         </div> </div>																	
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<b>Mme. M. van der Drift</b>																	



III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	US, A, 4174295 (BARGIGIA et al.) 13 November 1979 see abstract; column 2, line 58 - column 3, line 3; column 3, lines 8-15; column 3, lines 44-50; column 5, lines 26-40; example 7; claim 1	6,7
A	US, A, 3490923 (B.J. EISEMAN et al.) 20 January 1970 see the whole document  -----	1-10

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

**GB 9100133**

**SA 44267**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on 04/06/91  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 9007333	12-07-90	None	
US-A- 4352789	05-10-82	None	
US-A- 4174295	13-11-79	DE-A- 2736500	16-02-78
		FR-A, B 2361454	10-03-78
		GB-A- 1529429	18-10-78
		JP-A- 53040693	13-04-78
		NL-A- 7708731	15-02-78
US-A- 3490923	20-01-70	None	

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82